REMARKS

The specification is amended above to change the title and insert a reference to related cases.

Several obvious typographical errors are corrected on pages 2, 64, 68, 76 and 81.

Claims 1 - 10 (inclusive), 20, 21, 24-35 (inclusive), 37 and 38, are cancelled without prejudice to future continuing applications, to remove claims of the prior parent case.

Claims 11-19, 22-23 and 36 are amended above to reformat the claims in view of the cancelled claims, and to correct a typographical error in claims 36.

No amendment of inventorship is necessitated by these amendments.

Early allowance of the claims is requested. Should the Examiner believe that a conference with applicants' attorney would advance prosecution of this application, the Examiner is respectfully invited to call applicants' attorney at the number below.

Respectfully submitted,

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Mark-up of the Claims Showing Changes Made

11. (AMENDED) ~~A~~ **An isolated** DNA which comprises a DNA having a nucleotide sequence coding for **an ependymin-like protein having an amino acid sequence represented by SEQ ID NO:1, SEQ ID NO:2 or SEQ ID NO:3, or a substantial equivalent thereto, or a salt thereof** ~~the protein according to claim 1 or 2~~.

12. (AMENDED) The **isolated** DNA according to claim 11, which comprises a nucleotide sequence represented by SEQ ID NO:18, SEQ ID NO:19 or SEQ ID NO:20.

13. (AMENDED) ~~A~~ **An isolated** DNA which comprises a DNA having a nucleotide sequence coding for **a** ~~the precursor~~ protein ~~according to claim 9~~ **having an amino acid sequence represented by SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12 or SEQ ID NO:13, or a substantial equivalent thereto**.

14. (AMENDED) The **isolated** DNA according to claim 13 which comprises a nucleotide sequence represented by SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29 or SEQ ID NO: 30.

15. (AMENDED) ~~A~~ **An isolated** DNA which comprises a DNA having a nucleotide sequence coding for ~~the~~ **a** signal peptide **comprising an amino acid sequence represented by SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16 or SEQ ID NO:17, or a substantial equivalent thereto** ~~according to claim 10~~.

16. (AMENDED) The **isolated** DNA according to claim 15, which comprises a nucleotide sequence represented by SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33 or SEQ ID NO:34.

17. (AMENDED) ~~A~~ **An expressible** recombinant vector comprising the DNA according to claim 11.

18. (AMENDED) A ~~transformant~~ **host cell** which is transformed with the recombinant vector of claim 17.

19. (AMENDED) A method for producing **an ependymin-like protein having an amino acid sequence represented by SEQ ID NO:1, SEQ ID NO:2 or SEQ ID NO:3, or a substantial equivalent thereto,** ~~the protein according to claim 1 or 2~~ or a salt thereof, which comprises cultivating the ~~transformant~~ **host cell** according to claim 18 under conditions **and for sufficient time** suitable to express and accumulate ~~the~~ **said** protein ~~according to claim 1 or 2 or a salt thereof~~, and collecting the same.

22. (AMENDED) A pharmaceutical composition which comprises the DNA according to claim 11 **and a pharmaceutically acceptable carrier, excipient or diluent**.

23. (AMENDED) **A method for making a** ~~The~~ pharmaceutical composition ~~according to claim 22,~~ which is a therapeutic or prophylactic agent for Alzheimer's disease, Parkington's disease, Huntington's disease, amyotrophic lateral sclerosis, dementia or cerebellar degeneration **said method comprising combining a therapeutic amount of the DNA of Claim 11 with pharmaceutically acceptable carrier, excipient or diluent**.

36. (AMENDED) A method for treating or preventing Alzheimer's disease, **Parkinson's** ~~Parkingson's~~ disease, Huntington's disease, amyotrophic lateral sclerosis, dementia or cerebellar degeneration in a mammal which comprises administering an effective amount of the DNA according to claim 11 or a salt thereof to said mammal.

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as an entity comprising two kinds of proteins whose expression was increased after learning in the brain of goldfish as assayed by a double-labeling technique using [^{3}H]valine and [^{14}C]valine (Shashoua, V. E., Science, 193, 1264-1266 (1976)). Early immunohistological distribution studies (Shashoua, V. E., Brain Research, 122, 113-124 (1977), Benowitz, L. I. and Shashoua, V. E., Brain Research, 136, 227-242 (1977)) revealed that those proteins occurred in high concentrations in the ependymal zone (the cellular membrane lining the brain ventricles) and accordingly they were named ependymin β and ependymin γ, respectively. However, it was subsequently suggested that those proteins were secretory proteins which were secreted into the cerebrospinal fluid (Shashoua, V. E. Brain Research, 166, 349-358 (1979); Shashoua, V. E. Neurochem. Res., 6, 1129-1147 (1981)) and more detailed immunohistological investigation endorsed the suggestion by the detection of ependymin in high concentrations in the mesencephalic structures and cerebrospinal fluid (Schmidt, R. and Lapp, H., Neurochem. Int., 10, 383-390 (1987).

Ependymin β and ependymin γ were initially considered to be mutually distinct proteins because they gave molecular masses of 35kDa and 30kDa, respectively, on SDS-PAGE but it was later discovered that they are proteins identical in amino acid sequence and only dissimilar in sugar chain content (Schmidt, R. and Shashoua, V. E., Journal of Neurochemistry, 40, 652-660, (1983)). Moreover, it was reported that those proteins formed dimers and ~~has~~ have a sugar chain content of at least 5% (Shashoua, V. E., Cell. Mol. Neurobiol., 5, 183-207 (1985)).

Based on the above series of research findings, ependymin had come to be considered to be associated with the learning and memory processes. For example,

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oligonucleotide or a derivative thereof are shown below.

(1) Pharmaceutical composition

The protein, etc. of the present invention and the DNA of the present invention are useful as drugs such as therapeutic or prophylactic agent for a defect of the gene coding for the protein of the present invention and associated diseases therewith, a dysfunction of the protein of the present invention and associated diseases therewith and so on. Specifically, the protein, etc. of the present invention or the DNA of the present invention are useful as drugs such as a therapeutic or prophylactic agent for Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral scleorosis, dementia or cerebellar degeneration.

For example, when there is a patient in whom the protein, etc. of the present invention in the body cannot function sufficiently or normally because of its decrease or defect, the protein, etc. of the present invention of the patient can be expected to function sufficiently or normally by:

(a) administering the DNA coding for the protein, etc. of the present invention to the patient to express it;

(b) inserting the DNA coding for the protein, etc. of the present invention into cells to express it and transplanting the cells to the patient, or

(c) administering the protein, etc. of the present invention to the patient.

For example, the protein, etc. of the present invention can be used orally in the form of tablets which may be sugar coated as necessary, capsules, elixirs, microcapsules etc., or non-orally in the form of injectable preparations such as aseptic solutions and suspensions in water or other pharmaceutically

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detected or a mutation of the DNA is detected by the PCR-SSCP assay, it may lead, with high probability, to the diagnosis of Alzheimer's disease, Parkinson's disease, Huntigton's disease, amyotrophic lateral sclerosis, dementia or cerebellar degeneration.

(3) Quantitative determination of the protein of the present invention, its partial peptide or a salt thereof

The antibody of the present invention is capable of specifically recognizing the protein, etc. of the present invention and, accordingly, it can be used for quantitative determination of the protein, etc. of the present invention in test liquid samples and particularly for quantitative determination by sandwich immunoassays.

Thus, the present invention provides, for example, the following methods:

(i) a quantitative determination of the protein, etc. of the present invention in a test liquid sample, which comprises

(a) competitively reacting the test liquid sample and a labeled protein, etc. of the present invention with the antibody of the present invention, and

(b) measuring the ratio of the labeled protein, etc. of the present invention binding with the antibody; and

(ii) a quantitative determination of the protein, etc. of the present invention in a test liquid sample, which comprises

(a) reacting the test liquid sample with an antibody immobilized on an insoluble carrier and another labeled antibody simultaneously or continuously, and

(b) measuring the activity of the labeling agent on the insoluble carrier,

wherein one antibody is capable of recognizing the N-terminal region of the protein, etc. of the present

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suspending the protein, its partial peptide or a salt thereof of the present invention (hereinafter sometimes referred to as the protein, etc. of the invention) in a screening buffer. The screening buffer may be any buffer that does not affect the contact of the protein, etc. of the present invention with the nerve cells or nerve tissues (for example, phosphate buffer and Tris-HCl buffer within the pH range of about 4-10 (preferably pH about 6-8). The contact time is generally about 1-10 days and preferably about 7-10 days. The contacting temperature is generally about 37°C.

The nerve-extending or neuro-regenerative activity in the central nerve system or gliacyte stimulating activity of the protein, etc. of the present invention can be assayed by the conventional technique, for example by measuring the elongation of the optic nerve axon or determining the change in intracellular Ca^{2+} concentration.

Thus, the test compound which promotes physiological activities, such as a nerve-extending or neuro-regenerative activity or a gliacyte stimulating activity, by not less than about 20%, preferably not less than about 30%, more preferably not less than about 50%, and most preferably not less than about 70% in case (ii) as compared with case (i) can be selected as a candidate compound which promotes the function of the protein, etc. of the present invention.

To carry the screening method (b) of the present invention into practice, the protein, etc. of the present invention and the test compound are administered to a vertebrate by the intravenous, subcutaneous, intramuscular or oral route. The dosage of the protein, etc. of the present invention for oral administration to human or chimpanzee (body weight 60 kg) is about 0.1 to 100 mg, preferably about 1.0 to 50

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coding for the protein, etc. of the present invention and promotes the expression of the DNA, the mRNA or the protein, etc. of the present invention is capable of promoting the function of the protein, etc. of the present invention in vivo. Therefore, the oligonucleotide or a derivative thereof is used for a prophylactic or therapeutic agent for various diseases such as Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral scleorosis, dementia and cerebellar degeneration.

When the oligonucleotide or a derivative thereof is used for the prophylactic or therapeutic composition as mentioned above, it can be formulated in the same way as the prophylactic or therapeutic agent containing the protein or the DNA of the present invention and can be administered to mammals.

Because the thus-obtained preparation is safe and of low toxicity, it can be administered to mammals (e.g., human, mouse, rat, rabbit, sheep, pig, bovine, horse, cat, dog, monkey, champanzee, etc.).

The DNA may be used alone or after inserting it into a suitable vector such as retrovirus vector, adenovirus vector, adenovirus-associated virus vector, pox virus etc. followed by administering the product vector to a mammal by a conventional means. The oligonucleotide or a derivative thereof can also be administered oligonucleotide or a derivative thereof with physiologically acceptable carriers such as adjuvants to assist in uptake, by "gene" gun or by a catheter such as a catheter with a hydrogel.

In addition, the oligonucleotide or a derivative thereof can be used as a diagnostic oligonucleotide probe for investigating the presence of the DNA of the present invention or the status of its expression in various tissues and cells.